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Obesity and harmful alcohol consumption are predictors for advanced liver disease in the disease management program for type 2 diabetes

Maurice Michel[1,2] | Michelle Doll[1,2] | Nastasia Albert[1,2] | Marc Morgenstern[3] | Andreas Behr[4] | Stefan Maxeiner[4] | Christian Labenz[1,2] | Peter R. Galle[1,2] | Jörn M. Schattenberg[1,2,5,6]

[1]Metabolic Liver Research Program, I. Department of Medicine, University Medical Centre Mainz, Mainz, Germany

[2]I. Department of Medicine, University Medical Centre Mainz, Mainz, Germany

[3]Diabetology Practice Mainz, Mainz, Germany

[4]Diabetology and Family Practice, Bad Kreuznach, Germany

[5]Department of Internal Medicine II, Saarland University Medical Centre, Homburg, Germany

[6]University of the Saarland, Saarbrücken, Germany

Correspondence
Jörn M. Schattenberg, Metabolic Liver Research Program, I. Department of Medicine, University Medical Centre Mainz, Mainz, Germany.
Email: joern.schattenberg@unimedizin-mainz.de

Abstract

Background: Type 2 diabetes mellitus (T2DM) is a major risk factor for advanced liver disease. The aim of this prospective cohort study was to assess the prevalence and associated risk factors of liver fibrosis and cirrhosis in primary care centers participating in the diabetes disease management program (DMP) in Germany.

Methods: A total of 175 participants with the diagnosis of T2DM were enrolled in two primary care centers. Steatotic liver disease (SLD; hepatic steatosis, ≥275 dB/m), fibrosis (≥8 kPa), and cirrhosis (≥15 kPa) were assessed non-invasively using vibration-controlled transient elastography. Multivariable logistic regression analysis was performed to identify clinical predictors of fibrosis and cirrhosis. The AUDIT questionnaire was used to screen for alcohol consumption, and a score ≥8 was considered harmful alcohol consumption.

Results: The majority of participants were male (62%), and the median age was 66 years (interquartile range 59; 71). The median body mass index was 31.1 kg/m^2, with 58.9% of the participants being obese. Harmful alcohol consumption was prevalent in 8.0% and 20.0% of the entire cohort and in those with cirrhosis, respectively. The prevalence of SLD, fibrosis, and cirrhosis was 77.1%, 42.3%, and 12.0%, respectively. In multivariable logistic regression analysis, obesity, and harmful alcohol consumption were associated with the highest odds of fibrosis (odds ratio [OR] 5.198, 95% confidence interval [CI] 2.269–11.908) and cirrhosis (OR 5.615, 95% CI 1.274–24.756), respectively.

Conclusion: The prevalence of fibrosis and cirrhosis in patients seen in the diabetes DMP in Germany is high. Obesity and harmful alcohol consumption increase the risk of fibrosis and cirrhosis in people with T2DM. Screening for advanced liver disease and associated risk factors within the DMP program may reduce the liver disease burden in this high-risk population.

KEYWORDS
alcohol consumption, cirrhosis, liver fibrosis, obesity, steatotic liver disease, type 2 diabetes, VCTE

INTRODUCTION

Steatotic liver disease (SLD) is highly prevalent in the population and metabolic dysfunction-associated steatotic liver disease (MASLD) shows an estimated prevalence of 30% globally.[1–3] The most prevalent comorbidities of MASLD are type 2 diabetes mellitus (T2DM) and obesity with a high risk of disease progression resulting in fibrosis and cirrhosis.[4,5] Liver fibrosis is slowly progressive and the stage of fibrosis has prognostic relevance and is associated with an increase in liver-related complications, including cirrhosis and hepatocellular carcinoma (HCC), reduced health-related quality of life, increased socioeconomic costs, and higher mortality.[5–7] Additionally, harmful alcohol consumption is a major risk factor that augments disease progression and the development of advanced liver disease, especially in people with T2DM.[8,9] Importantly, alcohol consumption may be underreported in patients with MASLD.[10] To highlight that metabolic comorbidities and alcohol consumption can both contribute to liver fibrogenesis, MASLD with increased alcohol consumption (MetALD) was recently suggested as a relevant subgroup of patients with SLD.[2]

In Germany, a disease management program (DMP) has been implemented to allow for best practice patterns in people with T2DM. The DMP expands regular medical care by financing standardized diagnostic and management aiming to reduce terminal complications of T2DM by screening for comorbidities, including arterial hypertension (art. HTN), cardiovascular disease (CVD), chronic kidney disease (CKD), neuropathy, retinopathy, and diabetic foot syndrome (DFS).[11] This aligns with best practice recommendations and referral pathways.[12] Until today, testing for liver disease within the DMP is not established, albeit recommendations in national and international guidelines.[13–15]

Given the availability of effective preventive measures to decrease the risk of end-stage liver disease and cancer related to SLD, non-invasive screening for liver fibrosis and cirrhosis in people with T2DM is encouraged in German guidelines.[14] Ultrasound-based transient elastography, such as vibration-controlled transient elastography (VCTE, Fibroscan®), may aid in the initial risk stratification and predict overall mortality.[16]

Currently, no prospectively collected data on the prevalence of liver fibrosis and cirrhosis in people with T2DM enrolled in the DMP are available from Germany. Despite broad consensus on the requirement of multi-stakeholder approaches, including endocrinologists, diabetologists, and nutritionists, solid knowledge of the disease prevalence and diagnostic tests is needed for patients to be managed according to current knowledge.[12,17] This study aimed to determine the prevalence of advanced liver disease and associated risk factors using a VCTE-based screening strategy in this best-practice care pathway in Germany.

Key summary

Summarise the established knowledge on this subject

- Type 2 diabetes mellitus (T2DM) is associated with end-organ injury and a major risk factor for advanced liver disease with worse liver-related outcomes.
- Despite the high relevance of advanced liver disease in people with T2DM, it remains unconsidered in the routine screening of T2DM-related comorbidities in the diabetes disease management program (DMP) in Germany.
- The prevalence of advanced liver disease and associated risk factors using a VCTE-based screening approach have not been studied in primary care centers participating in the diabetes DMP in Germany so far.

What are the significant and/or new findings of this study?

- The prevalence of advanced liver disease is high in people with T2DM in the diabetes DMP in Germany.
- Obesity and harmful alcohol consumption increase the odds of having advanced liver disease from MetALD in this high-risk population.
- Vibration-controlled transient elastography may aid in the risk assessment of liver disease in this DMP.
- Considering the assessment of liver disease and associated risk factors in the diabetes DMP may reduce liver-related comorbidities in people with T2DM.

METHODS

Study cohort

A total of 178 study participants treated for T2DM were enrolled prospectively at the (1) Diabetology Practice Mainz and (2) Diabetology and Family Practice Bad Kreuznach as part of their routine care visits within the DMP between 2019 and 2021. Participants had to be at least 18 years of age and provide written informed consent before study inclusion. Individuals with an already-known diagnosis of liver cirrhosis were not eligible for study inclusion. Information on liver-related risk factors other than alcohol consumption and metabolic-derived, that is viral hepatitis, was retrieved from the medical records. Since population-based screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) is available in Germany, we did not include additional testing for these at study inclusion. Three

participants were excluded due to missing or invalid VCTE data, and 175 individuals were included in the final analysis.

Definition of steatotic liver disease, fibrosis, and cirrhosis

SLD, fibrosis, and cirrhosis were assessed using VCTE (Fibroscan® 430 mini) with the use of either an M or XL probe according to the manufacturer's guidance. A controlled attenuation parameter (CAP) of ≥275 dB/m was considered steatosis and thus provided evidence of SLD according to current practice guidelines.[2,18] Significant fibrosis, advanced fibrosis, and cirrhosis were defined as a liver stiffness measurement (LSM) of ≥8, ≥12, and ≥15 kPa, respectively, according to national practice guidelines and recent literature.[14,19] MASLD and alcohol-related liver disease (ALD) within the umbrella term SLD were defined according to a consensus statement on the new nomenclature.[2] Harmful alcohol consumption was assessed using the AUDIT questionnaire and defined as a cutoff ≥8.[20] Participants with steatosis and an AUDIT ≥8 were considered to have ALD. An additional surrogate score of SLD included the fatty liver index (FLI) with a cut-off of ≥60.[21]

Definition of baseline characteristics

The patient history, anthropometric measures, and biochemical profiles were collected at baseline on the day of the VCTE scan performed by MD and NA. Body mass index (BMI, kg/m^2) was measured as weight (kg)/height (m^2), and obesity was defined as ≥30 kg/m^2. Comorbidities as well as medications related to T2DM were retrieved from the patient's history and medical records. In this context, CVD was defined if any of the following conditions were present in the history: coronary heart disease, myocardial infarction, atrial fibrillation, peripheral and central artery disease, thrombosis, or pulmonary embolism. The definition of CKD was based on the patient's history at study inclusion. High total cholesterol was defined as values ≥200 mg/dL. Gamma-glutamyl transferase (GGT) blood levels higher than 55 U/l were considered above the upper limit of normal. The metabolic syndrome (MetS) and its variables, including high triglycerides (TG, ≥150 mg/dL, or treatment of this condition), low high-density lipoprotein cholesterol (HDL, males <40 mg/dL; females <50 mg/dL), and art. HTN were defined according to the criteria of the International Diabetes Federation.[22]

Statistical analysis

Descriptive analysis of data is expressed as median values with interquartile ranges (IQR 25th; 75th) and mean with standard deviation (±SD) for normally distributed numerical data. Normal distribution of data was analyzed using the Shapiro–Wilk test. The Mann–Whitney *U* rank test was used to compare groups and to calculate differences between two groups with continuous variables. Categorical variables are presented as frequencies and percentages. The chi-square test was used to compare two or more patient groups. All tests were two-tailed; statistically significant values were defined as $p < 0.05$. Univariable logistic regression was used to examine the associations between the two variables. All variables with a *p*-value below 0.15 in the univariable analyses were included in a multivariable logistic regression model to examine associations with fibrosis and cirrhosis. Results of the multivariable analyses are presented unadjusted, adjusted for age and sex (Model 2), and additionally adjusted for harmful alcohol consumption (Model 3). IBM SPSS statistic version 23.0 (IBM Corp.) was used for all data analyses and statistical tests. Microsoft Excel 2016 (Microsoft Corp.) was used for all figures.

RESULTS

Baseline characteristics

The median age in the study cohort was 66.0 years (IQR 59.0; 71.0) and 37.7% ($n = 66$) were female. The median time since diagnosis of T2DM was 11.0 years (IQR 6.0; 18.3). Harmful alcohol consumption was prevalent in 8.0% ($n = 14$). Using VCTE, the median CAP (dB/m) and median LSM (kPa) were 328.0 (IQR 277.0; 367.0) and 7.2 (5.7; 10.7), respectively. The median BMI (kg/m^2) was 31.1 (IQR 27.7; 35.3), and the majority were obese ($n = 103$, 58.9%). The MetS was present in 58.3% ($n = 102$). Comorbidities, including CVD and CKD, were seen in 32.0% ($n = 56$) and 31.4% ($n = 55$), respectively. Viral hepatitis (HBV, HCV) was present in four (2.3%) participants. The majority (62.9%) were receiving metformin as part of the T2DM-related treatment. The baseline characteristics of the entire cohort are shown in Table 1.

Prevalence of steatotic liver disease, fibrosis, and cirrhosis

SLD was present in 77.1% ($n = 135$) of the participants. A total of 69.9% ($n = 121$) fulfilled the criteria of MASLD, and 12 (6.9%) were considered to have ALD. In two participants, no classification according to the subgroups of SLD was possible due to missing AUDIT data. The FLI identified a total of 80.7% ($n = 121$) with SLD (Table 1). At least significant fibrosis was detectable in 42.3% ($n = 74$) of the cohort and 12.0% ($n = 21$) of all participants had cirrhosis (Figure 1). Applying a higher cutoff of ≥12 kPa, the prevalence of advanced fibrosis was 18.3% ($n = 32$).

Comparison between T2DM with and without liver fibrosis or cirrhosis

Higher median CAP values were seen in fibrosis (CAP: 356.0 dB/m, IQR 302.8; 384.5) and cirrhosis (CAP: 363.0 dB/m, IQR 303.5;

TABLE 1 Baseline characteristics of the study cohort.

	Total cohort (n = 175)
Variables	
Age in years	66.0 (59.0; 71.0)
Time since diagnosis (years) n = 174	11.0 (6.0; 18.3)
Sex	
Female	66 (37.7)
Male	109 (62.3)
Harmful alcohol consumption (AUDIT ≥8) n = 173	14 (8.0)
VCTE	
CAP (dB/m)	328.0 (277.0; 367.0)
LSM (kPa)	7.2 (5.7; 10.7)
Steatotic liver disease	
SLD	135 (77.1)
MASLD n = 173	121 (69.9)
ALD n = 173	12 (6.9)
FLI ≥60 n = 150	121 (80.7)
Metabolic abnormalities	
BMI (kg/m^2)	31.1 (27.7; 35.3)
Obesity (≥30 kg/m^2)	103 (58.9)
High TC ≥200 mg/dL n = 173	74 (42.3)
High TG ≥150 mg/dL n = 171	96 (54.9)
Low HDL-cholesterol: Male <40 mg/dL, female <50 mg/dL	34 (19.4), 29 (16.6)
Art. HTN	153 (87.4)
MetS	102 (58.3)
Biochemical profile	
GGT n = 173	36.0 (26.0; 56.5)
TG n = 171	164.0 (113.0; 249.0)
TC n = 172	190.5 (155.5; 219.5), 189.9 (±46.8)
LDL n = 171	113.0 (82.0; 144.0), 113.0 (±40.7)
HDL n = 171	48.0 (39.0; 57.0)
Platelets n = 173	221.0 (191.5; 260.0)
HbA1c (%) n = 174	7.0 (6.5; 7.8)
>8.5	26 (14.9)
GFR n = 173	82.0 (66.6; 96.9), 81.3 (±23.8)
Comorbidities	
CVD	56 (32.0)
CKD	55 (31.4)
Retinopathy	15 (8.6)
Polyneuropathy	53 (30.3)
DFS	19 (10.9)
Viral hepatits (HBV, HCV)[a]	4 (2.3)
Medication	
Metformin	110 (62.9)
Insulin	94 (53.7)
SGLT-2 inhibitors	22 (12.6)
GLP-1 agonists	16 (9.1)
No treatment	16 (9.1)

Note: Data are expressed as numbers, median, percentage (%), and interquartile ranges (IQR 25th; 75th). Normally distributed numerical data is presented with mean values and standard deviation (±SD).

Abbreviations: ALD, alcohol-related liver disease; Art. HTN, arterial hypertension; BMI, body mass index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CVD, cardiovascular disease; DFS, diabetic foot syndrome; FLI, fatty liver index; GFR, glomerular filtration rate; GGT, gamma-glutamyl-transferase; HbA1c, hemoglobin A1c; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated liver disease; MetS, metabolic syndrome; SLD, steatotic liver disease; TC, total cholesterol; TG, triglycerides.

[a]HBV, n = 2; HCV, n = 2.

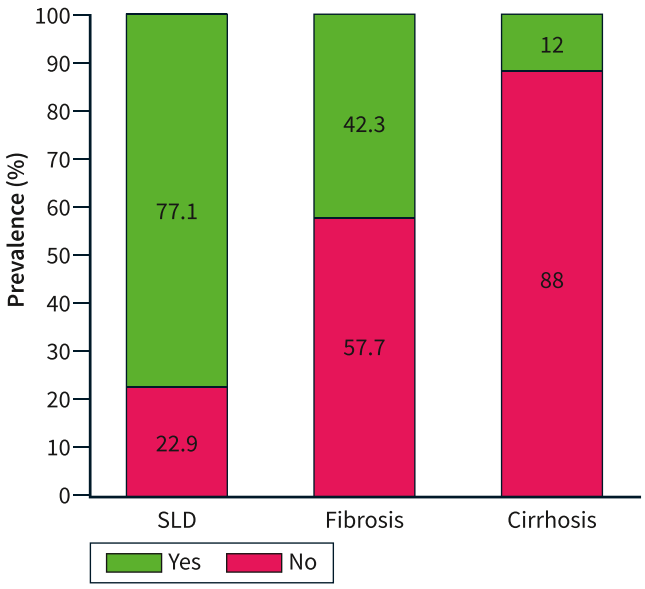

FIGURE 1 Prevalence of SLD, fibrosis, and cirrhosis in people with type 2 diabetes mellitus. SLD, fibrosis, and cirrhosis were detected in 77.1%, 42.3%, and 12.0%, respectively. SLD, steatotic liver disease.

378.5) respectively (Table 2). Harmful alcohol consumption was more prevalent in those with cirrhosis (n = 4, 20%) compared with those without cirrhosis (n = 10, 6.5%, p = 0.038). In terms of comorbidities, CVD was more prevalent in those with cirrhosis (61.9%). Median LSM values in individuals with SLD (7.8 kPa, IQR

TABLE 2 Comparison of characteristics between subgroups with fibrosis or cirrhosis.

	No fibrosis $n = 101$	Fibrosis $n = 74$	p	No cirrhosis $n = 154$	Cirrhosis $n = 21$	p
Variables						
Age in years	67.0 (58.5; 71.0)	65.0 (58.8; 70.3)	0.415	67.0 (58.8; 71.0)	64.0 (56.5; 70.5)	0.408
Time since diagnosis (years)	11.0 (6.0; 16.8)	12.0 (6.5; 21.0)	0.422	11.0 (5.0; 17.0)	14.0 (8.0; 22.5)	0.065
Sex			0.329			0.604
Female	35 (34.7)	31 (41.9)		57 (37.1)	9 (42.9)	
Male	66 (65.3)	43 (58.1)		97 (62.9)	12 (57.1)	
Harmful alcohol consumption (AUDIT ≥8)	6 (6.0)	8 (10.9)	0.238	10 (6.5)	4 (20.0)	**0.038**
VCTE						
CAP (dB/m)	311.0 (265.5; 354.0)	356.0 (302.8; 384.5)	**<0.001**	326.0 (275.5; 366.3)	363.0 (303.5; 378.5)	0.064
Metabolic abnormalities						
BMI (kg/m^2)	28.9 (26.9; 32.7)	34.9 (30.8; 40.3)	**<0.001**	30.5 (27.3; 34.6)	36.9 (33.6; 43.5)	**<0.001**
Obesity (≥30 kg/m^2)	43 (42.6)	60 (84.1)	**<0.001**	85 (55.2)	18 (85.7)	**0.008**
High TC ≥200 mg/dL	46 (46.0)	28 (38.4)	0.316	67 (44.1)	7 (33.3)	0.351
High TG ≥150 mg/dL	53 (53.3)	43 (59.7)	0.421	82 (54.6)	14 (66.7)	0.299
Art. HTN	82 (81.2)	71 (95.9)	**0.004**	132 (85.7)	21 (100)	0.064
MetS	42 (41.6)	60 (81.1)	**<0.001**	84 (54.5)	18 (85.7)	**0.007**
Biochemical profile						
GGT	31.0 (24.0; 41.0)	48.0 (31.8; 77.5)	**<0.001**	34.0 (25.0; 54.0)	50.0 (37.0; 81.0)	**0.002**
TG	162.0 (104.0; 237.0)	175.5 (122.5; 274.0)	0.112	162.0 (112.8; 245.0)	200.0 (119.5; 299.5)	0.395
TC	194.0 (154.0; 221.0); 191.8 (±49.7)	189.0 (160.5; 218.0); 187.5 (±49.7)	0.714	192.0 (159.0; 220.0); 191.3 (±47.1)	189.0 (145.5; 218.0); 180.3 (±44.2)	0.175
LDL	110.0 (84.3; 146.0); 115.2 (±42.2)	115.0 (73.0; 141.5); 110.1 (±38.6)	0.626	114.0 (85.0; 144.0); 114.4 (±40.9)	106.0 (71.0; 129.0); 103.2 (±37.9)	0.317
HDL	50.0 (39.0; 57.0)	47.5 (39.3; 54.5)	0.440	48.0 (39.8; 57.0)	47.0 (38.5; 54.0)	0.405
Platelets	221.0 (193.3; 266.0)	220.0 (187.0; 257.0)	0.581	221.0 (191.3; 266.0)	220.0 (186.0; 247.0)	0.741
HbA1c (%)	6.9 (6.5; 7.6)	7.4 (6.4; 8.5)	0.070	6.9 (6.4; 7.7)	7.7 (7.0; 8.6)	**0.012**
GFR	82.3 (66.9; 99.4); 82.7 (±23.2)	81.4 (65.9; 94.2); 79.4 (±24.7)	0.325	81.9 (66.2; 98.1); 81.4 (±24.1)	83.1 (69.8; 94.5); 80.4 (±22.4)	0.998
Comorbidities						
CVD	29 (28.7)	27 (36.5)	0.276	43 (27.9)	13 (61.9)	**0.002**
CKD	32 (31.7)	23 (31.1)	0.932	49 (31.8)	6 (28.6)	0.764
Retinopathy	4 (3.9)	11 (14.9)	**0.011**	10 (6.5)	5 (23.8)	**0.008**
Polyneuropathy	24 (23.8)	29 (39.2)	**0.028**	45 (29.2)	8 (38.1)	0.406
DFS	9 (8.9)	10 (13.5)	0.334	15 (9.7)	4 (19.0)	0.198
Viral hepatitis (HBV, HCV)	2 (1.9)	2 (2.7)	0.752	4 (2.6)	0 (0)	0.455
Medication						
Metformin	65 (64.4)	45 (60.8)	0.632	96 (62.3)	14 (66.7)	0.700
Insulin	48 (47.5)	46 (62.2)	0.055	78 (50.6)	16 (76.2)	**0.028**
SGLT-2 inhibitors	12 (11.9)	10 (13.5)	0.748	16 (10.4)	6 (28.6)	**0.018**

(Continues)

TABLE 2 (Continued)

	No fibrosis $n = 101$	Fibrosis $n = 74$	p	No cirrhosis $n = 154$	Cirrhosis $n = 21$	p
GLP-1 agonists	8 (7.9)	8 (10.8)	0.512	13 (8.4)	3 (14.3)	0.383
No treatment	13 (12.9)	3 (4.1)	**0.046**	16 (10.4)	0	0.121

Note: Data are expressed as numbers, median, percentage (%), or interquartile ranges (IQR 25th; 75th). Normally distributed numerical data is presented with mean values and standard deviation (±SD). Mann–Whitney *U* test and chi-square test were used to compare continuous and categorical values, respectively. Boldface indicates statistical significance. A p-value < 0.05 was considered statistically significant.

Abbreviations: Art. HTN, arterial hypertension; BMI, body mass index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CVD, cardiovascular disease; DFS, diabetic foot syndrome; GFR, glomerular filtration rate; GGT, gamma-glutamyl-transferase; HbA1c, hemoglobin A1c; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MetS, metabolic syndrome; TC, total cholesterol; TG, triglycerides.

6.0; 11.3, $p < 0.001$) were higher compared to those without SLD (5.9 kPa, IQR 4.5; 7.6) (Table S1). Furthermore, participants with an AUDIT ≥8 had a median LSM of 8.4 kPa (IQR 6.1; 17.3), with no significant difference to those with an AUDIT <8 (7.1 kPa, IQR 5.6; 10.5) (Table S2).

Predictors of liver fibrosis and cirrhosis

Univariable and multivariable logistic regression models were built to identify predictors of fibrosis and cirrhosis. Although the variable MetS showed a positive association with fibrosis and cirrhosis on univariable analyses, it was not included in the multivariable analyses to avoid multicollinearity. After adjustment for age, sex, and harmful alcohol consumption (AUDIT ≥8) (Model 3), obesity (odds ratio [OR] 5.198, 95% confidence interval [CI] 2.269, 11.908, $p < 0.001$) was associated with the highest odds of significant fibrosis along with art. HTN (OR 5.155, 95% CI 1.170, 22.075, $p = 0.030$), elevated levels of GGT (OR 1.025, 95% CI 1.011, 1.040, $p = 0.001$), and male sex (OR 2.403, 95% CI 1.067, 5.410, $p = 0.034$) (Table 3). Harmful alcohol consumption (AUDIT ≥8) (OR 5.615, 95% CI 1.274, 24.756, $p = 0.023$) was independently associated with cirrhosis in the multivariable analysis after adjustment for age and sex (Model 2) (Table 4). Obesity (OR 4.428, 95% CI 1.367, 14.348, $p = 0.013$) and harmful alcohol consumption (AUDIT ≥8) (OR 4.492, 95% CI 1.367, 14.348, $p = 0.029$) remained independently associated with advanced fibrosis (Table S3).

Effect of obesity on liver disease stages in T2DM

The prevalence of obesity was 68.9% in participants with SLD. An even higher number of participants were obese compared to non-obese when fibrosis (81.1%, $n = 60$ vs. 18.9%, $n = 14$, $p < 0.001$) or cirrhosis (85.7%, $n = 18$ vs. 14.3%, $n = 3$, $p = 0.008$) were present (Figure 2). The median CAP and LSM values were 356 dB/m ($p < 0.001$) and 11.3 kPa ($p < 0.001$), respectively, in obese participants. All characteristics and comparisons of participants with or without obesity are shown in Table S4.

DISCUSSION

Liver disease in people with T2DM is increasingly prevalent, with rising numbers of end-stage liver disease and HCC globally.[23] The underlying pathophysiological mechanisms are inflammation and fibrogenesis which lead to liver cirrhosis over time. The amount of liver fibrosis is a crucial determinant of liver-related outcomes and overall mortality. Recently, German guidelines have recommended screening for liver fibrosis, however, this is not routinely or uniformly done yet.[24] Therefore, we conducted a screening study to identify fibrosis and cirrhosis as well as associated risk factors in people with T2DM enrolled in the German DMP for T2DM using VCTE. In two primary care centers, we identified 10% of all participants with previously undiagnosed liver cirrhosis. In addition, almost half of the study population had at least significant fibrosis. Multivariable regression analyses identified obesity and harmful alcohol consumption as the most important additional risk factors for fibrosis and cirrhosis.

The current study highlights the feasibility of screening for liver disease in people with T2DM as part of the German DMP in primary care practices and details the prevalence of fibrosis and cirrhosis in this high-risk group. Obesity and other components of the MetS augmented the risk of T2DM leading to higher odds of fibrosis. That exponential increase in fibrosis in patients with T2DM and obesity is in line with previous findings.[19] Metabolic risk factors are also known to augment the risk of progression independent of the liver disease etiology.[25] Although a previous analysis showed a lower prevalence of fibrosis and liver cirrhosis in T2DM, participants with other liver disease etiologies than MASLD have been excluded.[19] However, the role of harmful alcohol consumption in liver disease cannot be underestimated and even moderate alcohol intake was associated with a higher risk of fibrosis progression and cirrhosis-related complications in those identified with MASLD.[26] In the current study, harmful alcohol consumption was present in the majority of participants with cirrhosis, and independently associated with advanced fibrosis and cirrhosis. These findings are in line with a previous analysis, highlighting the importance of alcohol as a major risk factor for liver disease progression and cirrhosis in people with T2DM.[9] As a result of the negative impact of alcohol consumption along with

TABLE 3 Univariable and multivariable logistic regression analysis of predictors of significant fibrosis.

	Significant fibrosis (≥8 kPa)											
				Multivariable analysis								
	Univariable analysis			Model 1			Model 2			Model 3		
Variable	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age in years	0.987	0.960, 1.016	0.379				1.009	0.972, 1.048	0.626	1.010	0.973, 1.049	0.594
Time since diagnosis	1.018	0.981, 1.056	0.341									
Sex, male	1.359	0.733, 2.521	0.330				2.104	0.960, 4.615	0.063	**2.403**	**1.067, 5.410**	**0.034**
Harmful alcohol consumption (AUDIT ≥8)	1.928	0.639, 5.820	0.244							1.973	0.520, 7.485	0.318
Obesity	**5.781**	**2.862, 11.674**	**<0.001**	**4.989**	**2.268, 10.973**	**<0.001**	**5.431**	**2.387, 12.355**	**<0.001**	**5.198**	**2.269, 11.908**	**<0.001**
High TC	0.730	0.395, 1.350	0.316									
High TG	1.287	0.696, 2.380	0.421									
Art. HTN	**5.484**	**1.558, 19.302**	**0.008**	**5.102**	**1.238, 21.016**	**0.024**	4.066	0.983, 16.816	0.053	**5.155**	**1.170, 22.705**	**0.030**
MetS	**6.020**	**2.979, 12.167**	**<0.001**									
Platelets	0.999	0.993, 1.005	0.706									
GGT	**1.022**	**1.010, 1.034**	**<0.001**	**1.022**	**1.009, 1.036**	**0.001**	**1.025**	**1.011, 1.039**	**0.001**	**1.025**	**1.011, 1.040**	**0.001**
HbA1c	**1.335**	**1.021, 1.746**	**0.035**	0.874	0.614, 1.244	0.455	0.811	0.561, 1.170	0.262	0.802	0.553, 1.163	0.244
Metformin	0.859	0.463, 1.597	0.632									
Insulin	**1.814**	**0.985, 3.342**	**0.056**	0.999	0.449, 2.222	0.998	0.977	0.431, 2.212	0.955	0.959	0.421, 2.183	0.920
No treatment	**0.286**	**0.078, 1.043**	**0.058**	0.526	0.117, 2.366	0.402	0.415	0.089, 1.932	0.262	0.332	0.066, 1.661	0.180

Note: MetS was not included in the multivariable analysis to avoid multicollinearity. With all factors showing a *p*-value < 1.5 in the univariable analysis, a multivariable regression model with different levels of adjustment was built. Boldface indicates statistical significance. A *p*-value < 0.05 was considered statistically significant. Model 1: Unadjusted, logistic regression model including the following variables: obesity, art. HTN, GGT, HbA1c, insulin, no treatment ($n = 172$). Model 2: Model 1 + adjusted for age and sex. Model 3: Model 1 + adjusted for age, sex, and AUDIT ≥8.

Abbreviations: Art. HTN, arterial hypertension; CI, confidence interval; GGT, gamma-glutamyl-transferase; HbA1c, hemoglobin A1c; MetS, metabolic syndrome; OR, odds ratio; TC, total cholesterol; TG, triglycerides.

TABLE 4 Univariable and multivariable logistic regression analysis of predictors of cirrhosis.

	Cirrhosis (≥15 kPa)								
	Univariable analysis			Multivariable analysis					
				Model 1			Model 2		
Variable	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age in years	0.979	0.939, 1.020	0.305				0.993	0.939, 1.051	0.812
Time since diagnosis	**1.045**	**0.099, 1.101**	**0.096**	1.035	0.968, 1.107	0.318	1.042	0.967, 1.123	0.279
Sex, male	1.276	0.507, 3.216	0.605				1.716	0.555, 5.303	0.348
Harmful alcohol consumption (AUDIT ≥8)	**3.575**	**1.005, 12.723**	**0.049**	**4.534**	**1.123, 18.314**	**0.034**	**5.615**	**1.274, 24.756**	**0.023**
Obesity	**4.871**	**1.378, 17.220**	**0.014**	3.124	0.815, 11.966	0.096	3.043	0.780, 11.870	0.109
High TC	0.634	0.242, 1.660	0.354						
High TG	1.659	0.633, 4.343	0.303						
MetS	**5.000**	**1.414, 17.675**	**0.012**						
Platelets	0.999	0.991, 1.008	0.842						
GGT	**1.006**	**1.000, 1.012**	**0.038**	1.004	0.998, 1.011	0.178	1.005	0.998, 1.011	0.163
HbA1c	**1.413**	**0.987, 2.022**	**0.059**	1.084	0.693, 1.698	0.723	1.039	0.657, 1.644	0.869
Metformin	1.208	0.461, 3.169	0.700						
Insulin	**3.118**	**1.088, 8.934**	**0.034**	2.206	0.531, 9.162	0.276	2.162	0.509, 9.178	0.296

Note: MetS was not included in the multivariable analysis to avoid multicollinearity. With all factors showing a *p*-value < 1.5 in the univariable analysis, a multivariable regression model adjusted for age and sex was built. Boldface indicates statistical significance. A *p*-value < 0.05 was considered statistically significant. Model 1: Unadjusted, logistic regression model including the variables: time since diagnosis, AUDIT ≥8, obesity, GGT, HbA1c, insulin ($n = 170$). Model 2: Model 1 + adjusted for age and sex.

Abbreviations: Art. HTN, arterial hypertension; CI, confidence interval; GGT, gamma-glutamyl-transferase; HbA1c, hemoglobin A1c; MetS, metabolic syndrome; OR, odds ratio; TC, total cholesterol; TG, triglycerides.

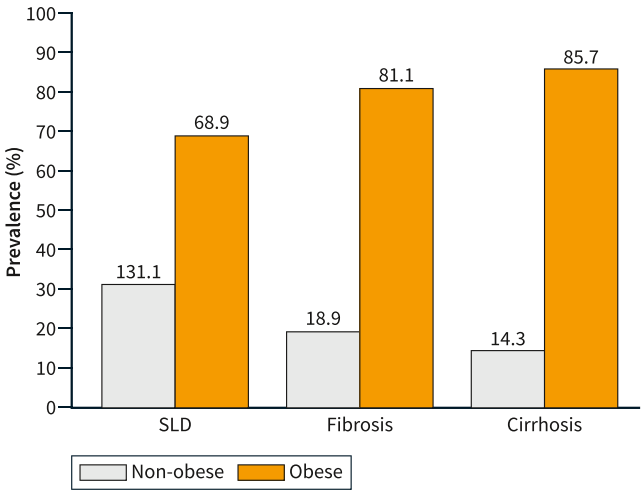

FIGURE 2 Prevalence of obesity among subgroups with steatotic liver disease, fibrosis, and cirrhosis.

metabolic risk factors on liver-related outcomes, the term MetALD has been implemented in the latest consensus statement on SLD to describe those patients sharing both risk factors.[2,27] While MetALD is distinct from ALD, it provides a framework for those with a predominantly negative metabolic profile and at least moderate alcohol consumption. In this analysis, we used the AUDIT questionnaire to define harmful alcohol consumption, and therefore no accurate estimate of MetALD can be given. It can be assumed that a specific cut-off for alcohol use in this population exists and prospective studies will have to determine this. Although the treatments for ALD and MASLD differ, we expect that the net effect of identifying previously undiagnosed cirrhosis is positive, even independent of the etiology. Therefore, it is recommended to discuss alcohol consumption in addition to modifiers of the metabolic risk in people with T2DM.

The German DMP is a platform to provide best practices to people with T2DM and optimally manage the associated comorbidities to prevent disease progression and impact morbidity and mortality cost-effectively.[11] Despite the high burden of liver disease in T2DM, the DMP only recognizes CKD, CVD, retinopathy, polyneuropathy, and DFS as T2DM-related comorbidities with recommendations for routine assessment.[13] Given that cirrhosis and HCC negatively affect health-related quality of life, increase the socioeconomic burden, and increase overall mortality, we strongly advocate screening for liver disease in this high-risk population.[5–7]

Current recommendations suggest the sequential use of the FIB-4 score.[18] However, the specificity of FIB-4 in the elderly population (>65 years) is low, with higher rates of false positive results, and the median age of our cohort was 66 years.[28] Only recently, Ajmera et al. were able to show that FIB-4 had the lowest diagnostic accuracy in detecting fibrosis in comparison to VCTE and MRI-based techniques

in people with T2DM.[19] While MRI-based techniques offer the highest diagnostic accuracy, the limited availability, and high costs reduce their applicability, especially in primary care settings.

Given the complexity of liver disease in T2DM with multiple in parts overlapping factors, including lifestyle habits, industrial fructose consumption, smoking, and viral hepatitis (HBV, HCV) that promote disease progression, a multi-stakeholder approach involving primary care, endocrinologists, and nutritionists besides hepatologists is necessary to provide optimal care.[12] Especially with the advent of emerging pharmacologic treatments of T2DM and obesity, which have shown an improvement in liver injury, require the expertise of endocrinologists and hepatologists alike.[29] Lifestyle interventions, that form the cornerstone of treatment and prevention of disease progression, need close surveillance of nutritionists along with primary care to achieve long-lasting effects.[30] Especially, those with harmful alcohol consumption need closer guidance to achieve and maintain abstinence to improve liver-related outcomes.[31] In addition, assessing genetic risk factors may complement the stratification of disease progression along VCTE and non-invasive markers in individual patients with SLD.[32] Knowledge about liver disease, using VCTE amongst others, would empower patients to act upon their risk profile by implementing lifestyle changes as recently seen in patients with ALD.[33] It can be expected that this will also be of benefit in patients with a high metabolic risk profile.

This study has several limitations. We chose VCTE for the non-invasive detection of liver disease, which has technical limitations, particularly in the obese population. Similar limitations apply to the CAP results as they are influenced by disease etiology, sex, BMI, T2DM, and level of transaminases, and thus under- or overreporting may have occurred.[34] Overall, the number of invalid exams in the current study was at an acceptable rate of less than 5%. When comparing CAP and FLI, similar rates of steatosis were seen. While liver biopsy is considered a reference standard, it is an invasive procedure and thus not suitable as a screening tool. Furthermore, liver enzymes are not included in the German DMP, and therefore FIB-4 was not available. Although recommended in current guidelines, the lack of FIB-4 is a limitation of our study.[14,15] Based on the high prevalence of advanced liver disease, the current data will support the discussion with payers around the implementation of the FIB-4 in the German DMP for T2DM. Although we assessed HBV or HCV infection in the patient's history, no additional screening was conducted at study inclusion and thus occult viral hepatitis cannot be ruled out entirely. The prevalence of HBV and HCV was higher compared to the general population in Western Europe, with the potential of a higher liver disease burden at baseline in comparison to other cohorts without viral hepatitis.[35] Moreover, we did not systematically exclude other causes of liver disease and it can be assumed that some cases of advanced liver disease are due to an unrecognized underlying chronic liver condition. Also, the majority of participants were over 50 years old and therefore the generalizability to younger populations with T2DM is limited. The current study was conducted bi-centric in a cross-sectional design in the federal state of Rhineland-Palatinate, and therefore the overall generalizability remains to be shown.

In summary, people with T2DM and additional risk factors, especially obesity and harmful alcohol consumption, enrolled in the best-practice DMP pathway in primary care in Germany are at a high risk of fibrosis and cirrhosis. The implementation of sensitive tests for risk stratification within the DMP would allow identifying the subgroup recommended for intensified management. We expect that screening for advanced liver disease within the DMP will lead to a positive impact by reducing the liver disease burden, improving health-related quality of life, and decreasing all-cause mortality.

AUTHOR CONTRIBUTIONS

Performed research: Maurice Michel, Michelle Doll, Nastasia Albert. Contributed to acquisition of data: Maurice Michel, Michelle Doll, Nastasia Albert, Marc Morgenstern, Andreas Behr, Stefan Maxeiner, Christian Labenz, Jörn M. Schattenberg; Designed the experiments and analyzed the data: Maurice Michel, Jörn M. Schattenberg; Contributed reagents/materials/analysis tools: Peter R. Galle, Jörn M. Schattenberg. Wrote the manuscript: Maurice Michel, Jörn M. Schattenberg. Revised and edited the manuscript: Maurice Michel, Christian Labenz, Peter R. Galle, Jörn M. Schattenberg. Statistical analysis: Maurice Michel, Jörn M. Schattenberg. All authors approved the final version of the manuscript and the authorship list. Guarantor of the article: Jörn M. Schattenberg.

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CONFLICT OF INTEREST STATEMENT

JMS reports Consultants: Apollo Endosurgery, Albireo Pharma Inc, Bayer, BMS, Boehringer Ingelheim, Echosens, Genfit, Gilead Sciences, GSK, Heel GmbH, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthcare GmbH. Research Funding: Gilead Sciences, Boehringer Ingelheim, Nordic Bioscience, Siemens Healthcare GmbH. Speaker Honorarium: MedPublico GmbH, Boehringer Ingelheim, Madrigal, Novo Nordisk; Stock Holder: AGED diagnostics, Hepta Bio. The other authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

ETHICS APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Landesaerztekammer Rhineland-Palatine Nr. 873.199.10 (7208).

CONSENT TO PARTICIPATE

Informed consent was obtained from all participants involved in the study.

CONSENT FOR PUBLICATION

All authors approved the final version of the manuscript and the authorship list.

ORCID

Maurice Michel https://orcid.org/0000-0001-7424-9085
Christian Labenz https://orcid.org/0000-0001-8390-9663
Jörn M. Schattenberg https://orcid.org/0000-0002-4224-4703

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